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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: THERAPEUTIC COMPOSITION FOR TREATMENT OF CANCER BY ARGININE DEPLETION

(57) Abstract: A therapeutic composition and a method for the treatment of cancer by depletion of arginine without systemic complications comprising an arginine decomposing enzyme and protein breakdown inhibitors, a nitric oxide donor, a pressor peptide, and prostacyclin. The composition may further include an amino acid mixture lacking arginine, an antidote for cyanide, blood plasma or its derivatives, and/or a preparation of arginine. The arginine decomposing enzyme may be modified to increase circulation half-life and can be type I liver arginase, or type II of human or animal, partially purified, or recombinant, or even bacterial origin. It may be administered as a drug or released from the patient's own tissue. Endogenous production of arginine, particularly via so-called intestinal-kidney axis, can be beneficially inhibited at several enzymatic steps, allowing for deeper reductions of circulating arginine. Different components of the composition may be administered separately, or in suitable mixtures, allowing for needed adjustments during the treatment.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/02342

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 38/43, 38/51; G01N 33/53; C12N 15/09, 9/00, 9/88

US CL : 424/94.1, 94.5; 435/7.71, 69.2, 183, 232

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/94.1, 94.5; 435/7.71, 69.2, 183, 232

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS STN, WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| Y | US 6,261,557 (TEPIC et al) 17 July 2001 (17:07.2001), entire publication. | 1, 4-14, and 17-31 |
| Y | Rao et al. Chemopreventive properties of a selective inducible nitric oxide synthase inhibitor in colon carcinogenesis, administered alone or in combination with celecoxib, a selective cyclooxygenase-2 inhibitor. Cancer Res. 2002 Jan 1;62(1):165-70. | 1, 4-14, and 17-31 |
| Y | Rao et al. Chemoprevention of colonic aberrant crypt foci by an inducible nitric oxide synthase-selective inhibitor. Carcinogenesis. 1999 Apr;20(4):641-4. | 1, 4-14, and 17-31 |
| A | Matthews et al. Nitric oxide-mediated regulation of chemosensitivity in cancer cells. J Natl Cancer Inst. 2001 Dec 19;93(24):1879-85. | 1, 4-14, and 17-31 |

☐ Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

03 September 2004 (03.09.2004)

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INTERNATIONAL SEARCH REPORT

international application no.

PCT/US03/02342

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1, 4-14, 17-31

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/02342

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Invention 1 Claim(s) 1, 4-14, and 17-31, drawn to a therapeutic composition comprising an arginine decomposing enzyme and an inhibitor of endogenous production of arginine.

Invention 2 Claim(s) 2 and 4-31, drawn to a therapeutic composition comprising an arginine decomposing enzyme and an inhibitor of intestinal-kidney axis.

Invention 3 Claim(s) 3, 4-14, 17-24, and 26-31, drawn to a therapeutic composition comprising an arginine decomposing enzyme and a nitric oxide donor.

Invention 4 Claim(s) 32 and 33, drawn to a pharmaceutical composition for the reduction of side-effects in cancer therapy.

Invention 5 Claim(s) 34-46, drawn to the use of NO donor for the manufacture of a medicament for the therapy of cancer.

The inventions listed as Inventions 1-4 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

No special technical feature exists between Inventions 1-5. Although Inventions 1-5 share a common property of being a therapeutic composition, they do not share a significant structural element since an inhibitor of endogenous production of arginine, an inhibitor of intestinal-kidney axis, and a nitric oxide donor are different chemical entities with different structural features. Furthermore, a therapeutic composition comprising arginine decarboxylase, which is an arginine decomposing enzyme, has already been taught in the prior art by US 6,261,557, wherein the said therapeutic composition comprising arginine decarboxylase is used for the treatment of cancer (see entire publication).